Funnel-Metadynamics and Solution NMR to Estimate Protein-Ligand Affinities

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KEYWORDS: Funnel metadynamics, solution NMR, absolute binding free energy, Human peroxiredoxin 5.

SUPPORTING INFORMATION

Figure S1

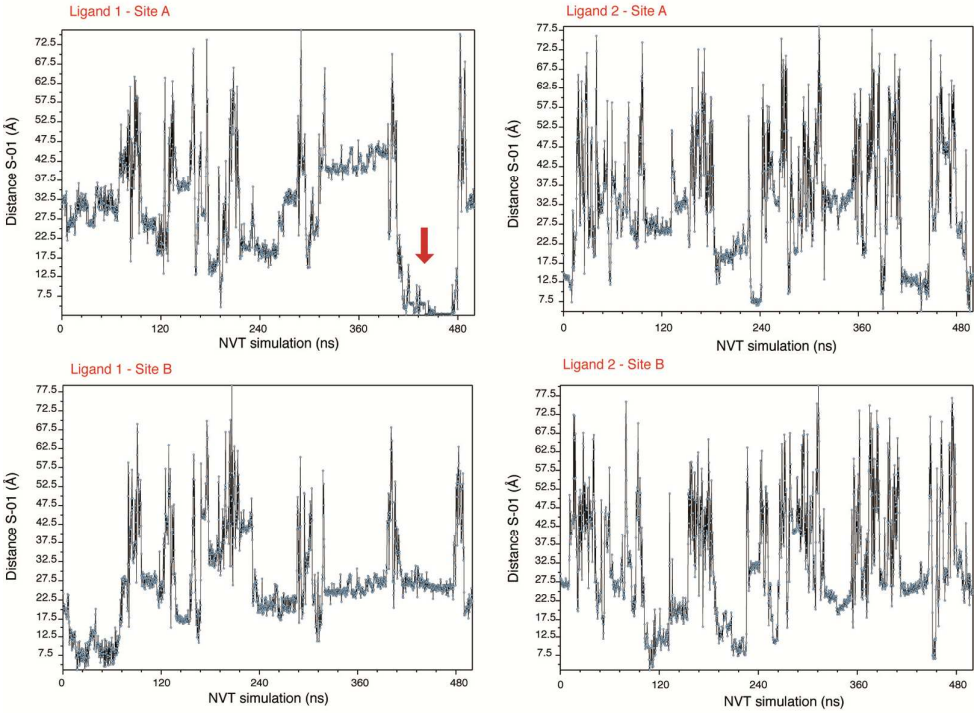

Figure S1 (continued)

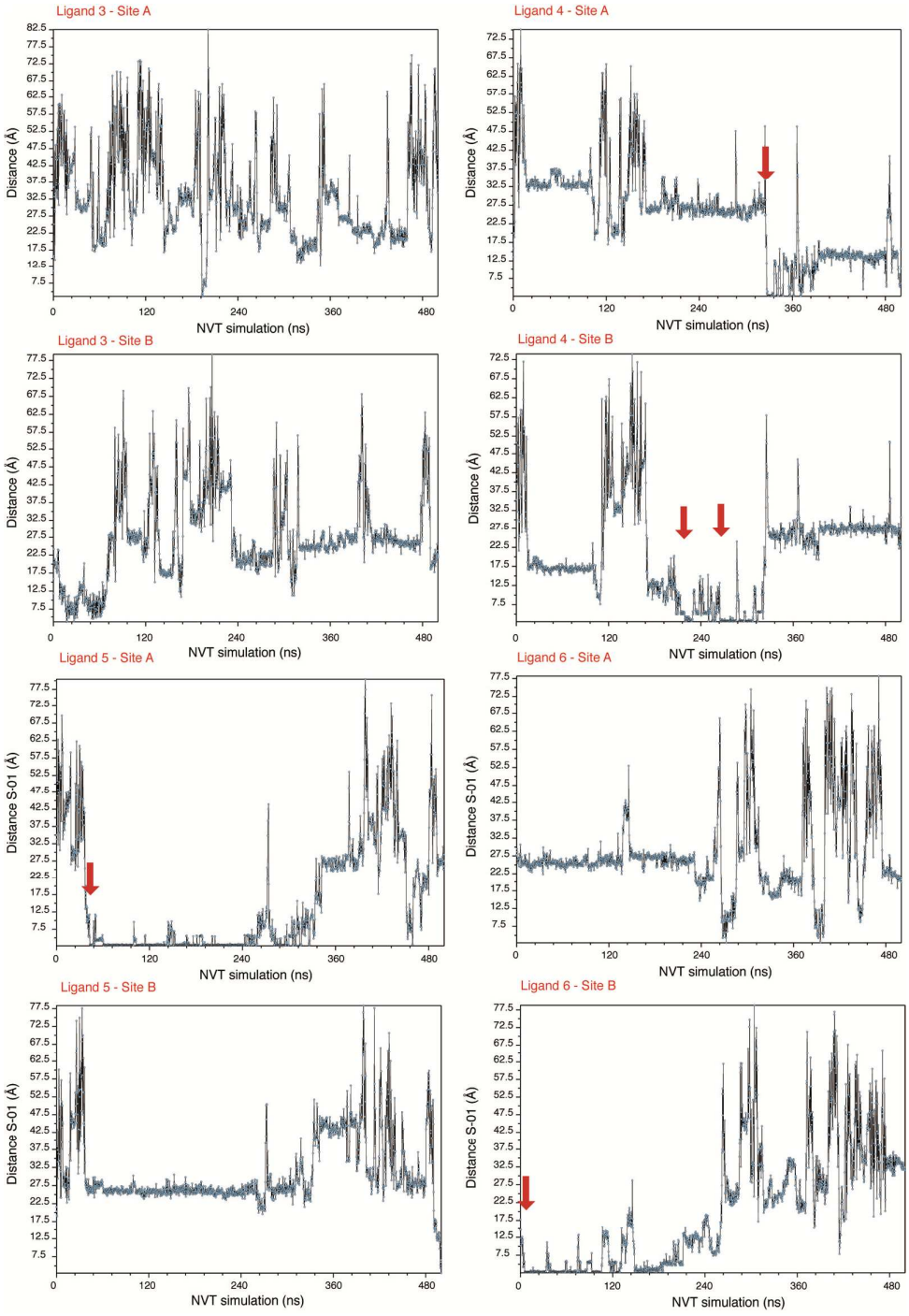

Figure S1. NVT ligand trajectories during an unbiaised NVT 500 ns dynamics into explicit solvent at high-concentration of 4-methylcatechol in the presence of equilibrated Human peroxiredoxin PRX5 crystal structure (PDB entry 3MNG.pdb[20]) in the TIP3P water model for the explicit solvent model[35]. Protein-ligand distances between the thiolate sulfur atom of each active sites of the homodimer (site A and site B) and the oxygen atom O1 of 4–methylcatechol are plotted against the NVT simulation time for each of the six 4-methylcatechol molecules (ligands 1 to 6). Red arrows indicate the beginning of a ligand-binding period to the active site of PRX5.

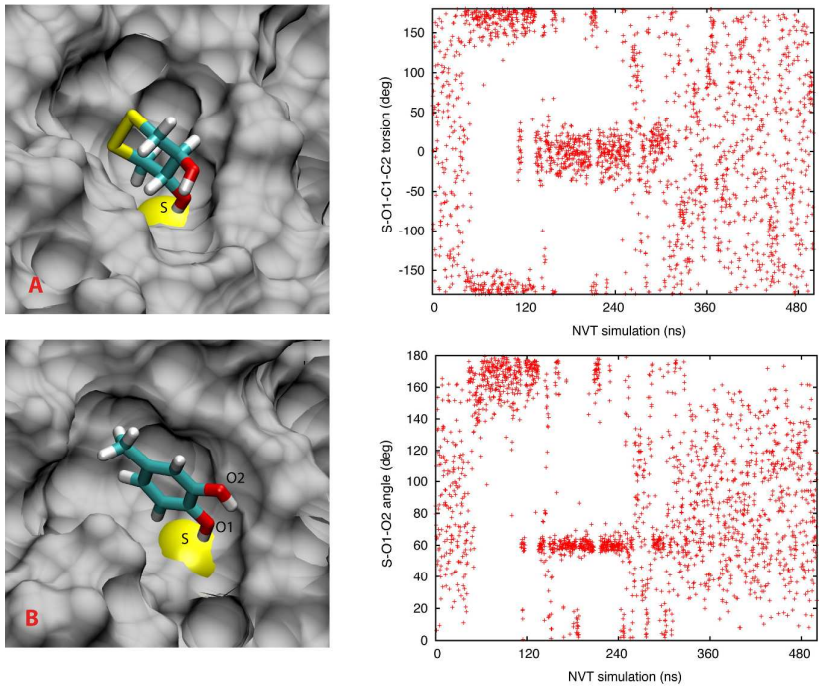

Figure S2. Ligands bound conformations to the active site of Human peroxiredoxin PRX5 and NVT trajectory during an unbiaised NVT 500 ns dynamics into explicit solvent at high-concentration of 4-methylcatechol. *A*: snapshot at 2ns of NVT of oxidized dithiothreiol (DTTox) H-bonded in the active site starting from the equilibrated crystal structure (PDB entry 3MNG.pdb[20]) in the TIP3P water model for the explicit solvent model[35]. The surface accessible to the solvent of PRX5 is represented in gray and the van der Waals sphere of Cys47 sulfur atom thiolate is drawn in yellow. *B*: Snaphot of 4-methylcatechol H-bounded in the active site at 90 ns of NVT (ligand 5 in Fig. S1). Protein to 4-methylcatechol ligand Cys47 S…O1-C1-C2 torsion (upper-right panel) and Cys47 S…O1-O2 angle is plotted along the NVT simulation time every 240 ps of dynamics. 4-Methylcatechol (ligand 5 of Fig. S1) binds first in the conformation shown in *B*, then exchanged with 2 H-bond conformers before unbinding (see the text).

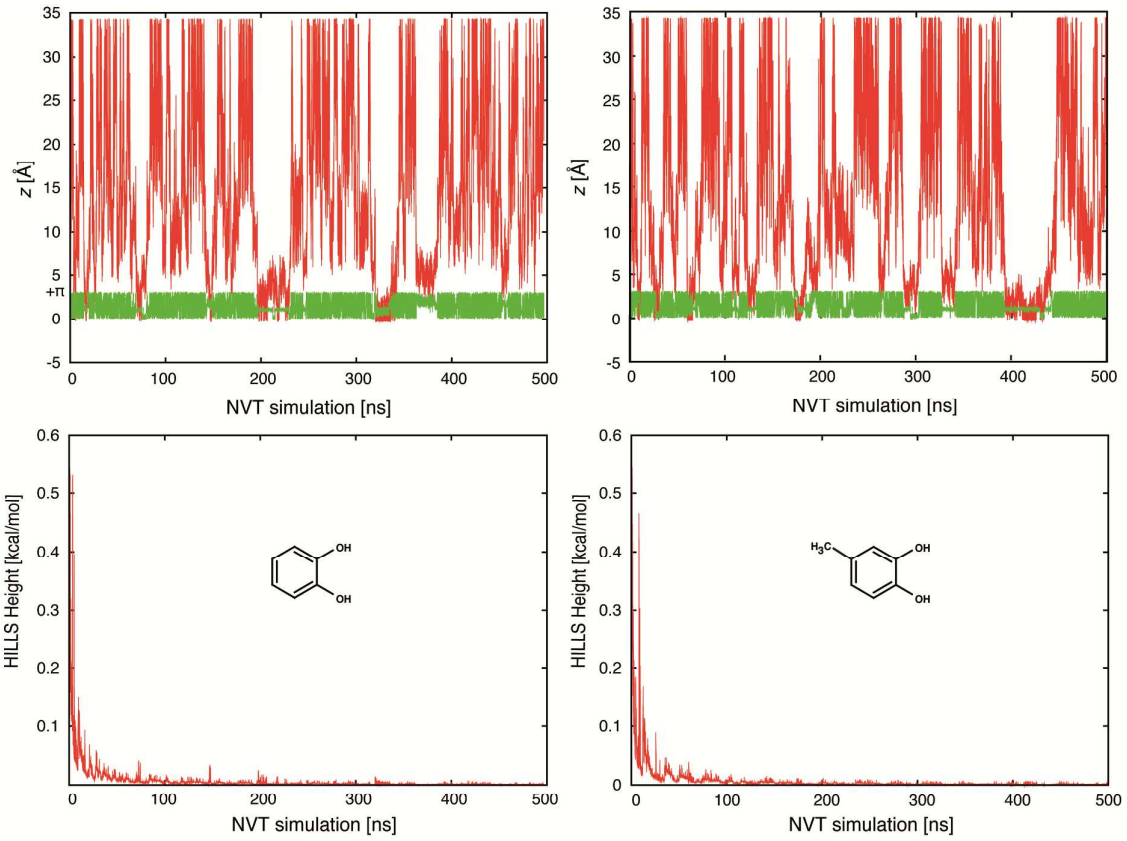

Figure S3. Funnel metadynamics trajectories of Human peroxiredoxin PRX5 in the presence of catechol (left panels) af 4-methylcatechol (right panels). Upper panels, red traces : position of the ligand projected on the funnel *Z*-axis in Å (CV1) as a function of the simulation time. The ligands sample the whole *Z*-axis dimension with the defined 0-34 Å limits of the fixed funnel external potential. The green traces indicate the collective variable Cys47 S…O1-O2 angle (CV3) reported in radian. Above *Z*-axis=18 Å, the ligand samples all conformations in the cylinder section of the funnel and interacts only with the solvent. Below 18 Å, the ligand interacts with the protein in the region of the active site. Binding periods correspond to the defined CV3 and the short CV1. Lower panels, Hills potentials deposition in kcal/mol along the simulation time indicating the progressing convergence where no energy depositions occur anymore.